OPEN PEER REVIEW REPORT 1

Name of journal: Neural Regeneration Research
Manuscript NO: NRR-D-21-00744
Title: Toxicities of Aβ and Tau are reciprocally enhanced in the Drosophila model
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Reviewer's country: USA

COMMENTS TO AUTHORS
The authors presented experimental evidence that Aβ and Tau mediated neurotoxicity are intertwined to each other, and this interaction are mediated (partly) through the activation of the JNK kinase in the Drosophila model. The paper addresses an interesting subject and highlights the role of this interaction as potential therapeutic target for the treatment of Alzheimer's disease.

However, there are few changes/concerns that should be addressed properly.
1) The manuscript should be proofread thoroughly for errors in grammar and spelling. For examples 'Material and Methods' should be written as 'Materials and Methods'. Indian University should be written as Indiana University. 'Secondary antibodies' should be 'secondary antibody'.

2) Author mentioned that Aβ is a short peptide composed of 40-42 amino acids but it can be composed of 39-42 amino acids.

3) The abbreviations need to be long form then uses the abbreviation.

4) Authors claimed that Aβ* expression did not result in obvious rough eye phenotype. However previous studies (PMID: 20084280; 25387847) showed that expression of Aβ42 in the eyes with the driver GMR-Gal4 results in a rough eye phenotype. How do authors correlate their findings with this previous report?

5) Authors made an assumption that Aβ can aggravate Tau hyperphosphorylation and toxicity, and reciprocally Tau also aggravates Aβ deposition, and this interaction can accelerate the progress of AD through Aβ-JNK-Tau-Aβ pathway. This is not unexpected because it is well known that cellular stress stimuli such as inflammatory cytokines, free radicals, and Aβ peptide can trigger JNK activation and Tau is a substrate of JNK. Moreover, the findings of this manuscript have confirmed previous reports of a connection between Aβ and Tau in drosophila model of Alzheimer's disease (PMID: 19782075). They further showed that inhibition of JNK with SP600125 lessens the effect of Aβ's and Tau toxicity which are again not surprising as they have been described previously (PMID: 22326868). However, the authors lack to really describe any new mechanism behind the findings, therefore the novelty of this article is somehow limited. The paper would greatly benefit if the authors could explore some of the other proposed mechanisms and try to understand their relative impact on the observed neurotoxicity.

6) Do author quantify the effect of the Aβ and Tau co-expression on BACE1 and gamma-secretase levels.

7) Quantitative analysis of several Western blot analysis was missing. Number of independent tests or number of flies per group has not mentioned elsewhere.

8) Student's t test will not be applicable for all data.